Gynecologic malignancies in female-to-male transgender patients: the need of original gender surveillance

Renata R. Urban, MD; Nelson N. H. Teng, MD, PhD; Daniel S. Kapp, MD, PhD

We report a case of uterine cancer and invasive cervical cancer, detected incidentally during the female-to-male sex reassignment surgery. The management of these patients is presented. Such individuals may not be receiving regular gynecologic care appropriate to their remaining genital organs; symptoms of malignant disease may be missed.

Key words: cancer screening, female-to-male, transgender

Cancers that involve either the uterine corpus or cervix were reported in more than 50,000 patients in 2009 in the United States. During the female-to-male sex reassignment process, the uterus, cervix, and ovaries are surgically removed. Such individuals are frequently in an amenorrheic state, which has been induced by hormone treatment with androgens.

There have been extremely few reports of gynecologic malignancies in testosterone-treated females to males, including 3 cases of ovarian cancers,[1,2] a single case of vaginal carcinoma,[3] and a single case of cervical carcinoma in situ.[4] So far, no cases of uterine carcinoma or invasive cervical carcinoma have been reported at the time of hysterectomy for female-to-male reassignment. We report on the evaluation and management of 1 individual with uterine cancer and another individual with invasive cervical cancer that we have treated over the past 2 years. In each case, the malignancy was detected incidentally during the sex reassignment process.

Case Reports

Patient A is a 54 year old transsexual male who began sex reassignment with androgen administration in 2000. Prior to this, he noted menarche at 12 years of age, and he had amenorrhea since 2000. He had not had prior intercourse with women since the age of 18 years. He denied any history of abnormal Papanicolaou smears or sexually transmitted diseases. His most recent normal Papanicolaou smear was in 2007. He denied any history of human immunodeficiency virus, intravenous drug use, or blood transfusions.

He continued the sex reassignment process with a bilateral mastectomy in 2005 and then presented for a hysterectomy in 2009. Prior to this, he had had vaginal spotting since 2007 that had been attributed to fibroids. He underwent a laparoscopic total hysterectomy and bilateral salpingo-oophorectomy in July 2009 at an outside hospital. The presence of an adenoma malignum was noted within the cervix. The tumor had 1-2 cm of horizontal spread and 0.9-1.1 cm of cervical stromal invasion. The resection margins were negative, but the tumor extended to within 1-2 mm of the margin. The tubes and ovaries were negative for tumor spread. No parametrial tissue or lymph nodes were taken.

The patient's postoperative course was uncomplicated. The patient was initially seen by Stanford physicians following this surgery; at that time, a biopsy of a lesion on the anterior vaginal cuff was negative for malignancy. Additional workup included a computerized axial tomography scan of the abdomen and pelvis, which revealed an indeterminate solitary pulmonary nodule at the right lung base and multiple sclerotic bone lesions in the pelvis. A subsequent bone scan was negative and positron emission tomography (PET) computerized tomography (CT) scan showed no PET avid lesions.

The patient began external beam pelvic radiation in September 2009 and completed his planned dose of 50.4 Gy. He then underwent 3 high-dose rate intracavitary treatments to the upper vagina. Concurrently he was started on chemotherapy with weekly cisplatin. Three months following completion of treatment, he was without evidence of disease.

Patient B is a 51 year old gravida 0 transsexual male who began the sex reassignment process in 2001. The patient had menarche at 13 years of age and denied any prior vaginal intercourse. His body mass index was 31 kg/m^2. He had no family history of breast, uterine, ovarian, or colon cancers. No routine gynecologic surveillance or Papanicolaou smears were obtained. After being amenorrheic for 7 years because of androgen therapy, he began having 2-3 months of vaginal bleeding. During a preoperative evaluation for a planned sex change operation, he was noted to have a cervical mass on speculum exam. This mass was biopsied and a diagnosis of cervical adenocarcinoma was made.

He then underwent radical hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy on Nov. 28, 2008, at an outside institution. Intraoperative findings included moderate adhesions around the uterus and a fungating cervical mass measuring approximately 5 × 2 cm. Pathology from this surgery revealed International Federation of Gynecology and Obstetrics stage IIIC grade 2 endometrioid adenocarcinoma of the uterus. Histologic

From the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Stanford University School of Medicine (Drs Urban and Teng), and Department of Radiation Oncology, Stanford Hospital and Clinics (Dr Kapp), Stanford, CA.

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Reprints: Renata Urban, MD, Division of Gynecologic Oncology, Stanford University Hospital and Clinic, 875 Blake Wilbur Dr., Stanford, CA 94305. rurban@stanford.edu.

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sections showed adenocarcinoma characterized predominately by endometrioid morphology with complex cribriform glandular architecture lined by cells with mild to moderately enlarged nuclei and increased mitotic activity. In some areas, the tumor exhibited villoglandular and papillary architecture; the majority of the tumor, however, demonstrated endometrioid morphology. Rare psammoma bodies were also identified. There was lymphovascular space invasion noted, positive parametrial involvement, and a positive vaginal cuff margin. Seven of 12 lymph nodes were positive for metastases. The ovaries and bilateral tubes were negative for involvement. Postoperatively, the patient had a CT abdomen/pelvis in December 2008, which revealed a 1.2 cm low density nodule in the spleen, a tiny pleural based nodule, and right ureteral double-J stent with downward migration. His CA 125 was 285 in December 2008.

The patient was first seen at Stanford University Medical Center in January 2009. Based on recommendations for systemic chemotherapy, the patient underwent 6 cycles of carboplatin and paclitaxel, which were completed in August 2009. He declined additional treatment with radiation. His CA 125 was 16 in September 2009. Unfortunately, at the time of this writing, this patient has evidence of recurrent disease at the vaginal cuff and paraaortic lymph nodes and is undergoing chemotherapy.

Comment

Approximately 1 in 30,000 women per year undergo sex reassignment treatment. During the hormonal treatment process, therapy with androgens induces a hypoestrogenic state leading to amenorrhea. Such changes lead to atrophy of the endometrium. Long-term androgen therapy has also been found to be associated with cervical atrophy. Although to the best of our knowledge, there has not previously been reported a case of uterine or invasive cervical carcinoma in a cohort of patients treated with high-dose androgens or in the female-to-male transgender population, the potential carcinogenic risks of androgens on endometrial tissue has been reviewed.[5] In addition, a recent epidemiological study suggested a possible association between testosterone exposure and endometrial cancer.[6] Of course, the possibility exists that the cancers we have reported were incidental findings, but occult malignancies have uncommonly been noted in recent studies. A summary of female-to-male transgender patients developing gynecologic malignancies, all but 1 of whom was reported to be on androgens, is presented in the Table.

Both of the patients in this case series presented with unusual cases of endometrial and cervical cancer. Patient A presented with adenoma malignum, which is an uncommon diagnosis. It has been found to account for only 1% of all cervical adenocarcinomas. Additionally, it is a challenging histologic diagnosis because of the interobserver variability in the histologic diagnosis of this neoplasm. The prognosis has also been difficult to assess, likely because of the variability in diagnosis of this specific cervical malignancy.

In retrospect, patient A could have been diagnosed prior to his surgery; his preceding symptoms of irregular vaginal spotting may have been incorrectly attributed to uterine fibroids. A pelvic examination with colposcopy and endocervical curettage may have detected the lesion, allowing the patient to undergo a more appropriate surgery of a radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection.

Patient B presented with a type II endometrial cancer. The tumor had features that were possibly suspicious for a serous uterine carcinoma; however, it was thought that the tumor did not exhibit the degree of cytologic atypia or architecture for such a diagnosis. The patient was not obese; however, he was nulliparous, which is less common in type II endometrial cancers. The patient had a gross cervical mass on examination, and additional evaluation with a magnetic resonance imaging scan of the pelvis could have been considered to rule out cervical and/or vaginal extension. If gross local extension was demonstrated, a different approach including preoperative radiation followed by surgery including complete pelvic and paraaortic lymphadenectomy could have been considered.

For patient B, adjuvant treatment consisted of systemic chemotherapy because recent phase III trials have demonstrated a survival advantage with chemotherapy vs radiation in the treatment of advanced endometrial cancer. In addition, volume-directed radiation therapy was recommended to the patient in accordance with the findings from the Gynecology Oncology Group 184. Despite recurrence at the vaginal cuff and paraaortic nodes, this patient may still benefit from directed radiation therapy to the nodal regions as well as additional vaginal brachytherapy.

The diagnosis of cervical or uterine cancer in such transgender individuals has important social and psychological impact. Despite undergoing significant medical and surgical treatment to undergo the female-to-male transgender process, each patient was now carrying the diagnosis of cancer of the female organs; in addition, each patient underwent their therapy under the case of gynecologic oncologists in offices and treatment areas surrounded by female patients. This likely contributed to a feeling of discomfort for each patient around providers, who were aware of the patient being transgender because of the patient's outward male appearance. Recognition of such discomfort in this rare group of patients is crucial because the prevalence of depression is quite high, and feelings of gender-based discrimination have been associated with an increased risk for suicide.[7] Providers should be aware of not only the confusion, which may develop over who should care for such patients, but also the logistic difficulty with insurance authorization because of coding error due to gender assignment.

Given the often long interval on androgen therapy prior to definitive surgery to the genital organs, routine screening of such patients based on their initial sex should be considered.[3] Recent guidelines by the Endocrine Society stress the monitoring for known health risks in the transsexual individual.[8] Although reassignment surgery prior to

TABLE
Gynecologic malignancies in female-to-male transsexuals: a review of the literature

Study, year	Transgender evaluation and treatment	Diagnosis of tumor	Initial cancer treatment	Pathology and stage	Subsequent treatment and outcome
Patient A, Hage et al, 2000[1]	Bilateral mastectomies, androgen therapy since 1980; hysterectomy 1981, multistaged phalloplasty 1990-1994	Presented with abdominal pain 17 y after hysterectomy; CT showed 22 × 17 cm ovarian tumor, CA125 4653 U/mL	Surgery: laparotomy, omentectomy, BSO, partial colectomy, biopsies	Stage IIIC papillary serous ovarian carcinoma	CDDP, paclitaxel, epirubicin; NED at second look at time of case report publication
Patient B, Hage et al, 2000[1]	Bilateral mastectomies 1998, androgen therapy since 1997	Pelvic ultrasound as preoperative evaluation for hysterectomy and BSO	Surgery: laparotomy, total hysterectomy, BSO, lymphadenectomy, omentectomy, biopsies	Stage IIC serous borderline tumor	No further treatment indicated; NED as of case report publication
Driak and Samudovsky, 2005[4]	Androgen therapy since 1999	Tumor detected incidentally at surgery in 2003	Surgery: total hysterectomy and BSO,bilateral mastectomies	Cervical squamous carcinoma in situ	No further treatment indicated; NED as of case report publication
Dizon et al, 2006[2]	Bilateral mastectomies, androgen therapy since 2001	Presented with increasing abdominal pain and distension; CT showed 14.5 × 27 ovarian tumor, CA 125 elevated	Surgery: laparotomy, total hysterectomy, BSO, omentectomy, lymphadenectomy, biopsies	Stage IIA well-differentiated endometrioid ovarian carcinoma	Carboplatin and paclitaxel; patient's tumor positive for androgen receptor-testosterone therapy discontinued; NED as of case report publication 1 y after treatment
Schenck et al, 2010[3]	Total hysterectomy with secondary phalloplasty	Presented with a tumor between the vagina and anus 18 y after sex reassignment surgery; exam showed 4 cm tumor in distal vagina, with infiltration of rectum and involvement of inguinal lymph nodes	Surgery refused; chemotherapy and local radiation	Stage IVA vaginal squamous cell carcinoma	Underwent total pelvic exenteration for progressive disease and vaginal fistula; postoperative, patient NED for 2 y prior to case publication
Patient A, current publication, 2010	Androgen therapy for 7 y, bilateral mastectomies	Vaginal bleeding noted for 2 y prior to hysterectomy	Surgery: laparotomy, total hysterectomy, BSO	Stage IB adenoma malignum of cervix, no lymph nodes sampled	CDDP plus pelvic EBRT, ICR, NED at time of case report
Patient B, current publication, 2010	Androgen therapy for 7 y	Presented with 2-3 months of vaginal bleeding, cervical mass noted on speculum exam	Surgery: radical hysterectomy, BSO, lymphadenectomy	Stage IIIC grade 2 endometrioid adenocarcinoma, involvement of parametrium and 7 lymph nodes	Carboplatin and paclitaxel, consideration for consolidation with radiation therapy

BSO, bilateral salpingo-oophorectomy; *CDDP*, cis-diaminedichloroplatinum; *EBRT*, external beam radiation therapy; *ICR*, intracavitary radiation therapy; *NED*, no evidence of disease.

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hormonal treatment may be preferable to avoid the potential risks of hormonally associated malignant transformation, at least 1 year of real life experience living as the desired gender role has been recommended.[8]

Hormonal treatment is recommended during this period before irreversible surgery is considered.[8] One aspect to consider in the care of these patients is screening for cervical dysplasia. Additionally, an evaluation of the endometrial lining when considering surgical transgender surgery should be included in the preoperative work-up. The approach to such evaluation requires an open communication between the physician and the patient. Despite the rarity of these conditions, we would recommend that such patients be considered for periodic screening for cervical dysplasia and that cervical and endometrial evaluation be performed in the preparation for surgical female-to-male transgender surgery. ■

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